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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,193	02/11/2005	Nobutaka Nakashima	081356-0232	4133

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EXAMINER	
POPA, ILEANA	
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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,193	NAKASHIMA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *18,24 and 32-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,11-14,19-21 and 25-28* is/are rejected.

7)☒ Claim(s) *4-10,15-17,22,23 and 29-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/11/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of the invention of Group I, drawn to an expression vector and transformed bacteria comprising the vector, and of the species of pTip-LNH1 having the nucleotide sequence of SEQ ID NO: 110, in the reply filed on 03/09/2007 is acknowledged.

Claims 18, 24, and 32-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-17, 19-23, and 25-31 are under examination.

Priority

2. It is acknowledged that a certified foreign priority paper has been received. However, an English translation has not been provided. Correction is required.

Should Applicants provide a certified translation of their foreign priority document to overcome the prior art rejection, Applicants should indicate whether the priority application is identical to the instant application, or if the priority application contains additional disclosure. If there is additional disclosure, a brief summary should be provided. Applicants should also indicate where support for each of the claim limitations (for the independent claims) can be found in the translated priority document by page and line number. If support is not found *in ipsis verbis*, clarification on the record may

be helpful to the examination process.

Oath/Declaration

3. The oath or declaration is defective because it does not identify the application to which it is directed. A new oath or declaration in compliance with 37 CFR 1.497(a) is required. See MPEP §§ 605.04.

Claim Objections

4. Claims 4-10, 15-17, 22, 23, and 29-31 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-10, 15-17, 22, 23, and 29-31 have not been further treated on the merits.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

6. Claims 11-14 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 25 recite the limitation "the host cell". There is insufficient antecedent basis for this limitation in claims 11 and 25. Claims 12-14 are rejected for being dependent from the rejected claim 11 and also for failing to further clarify the basis of the rejection.

7. Claims 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites the limitations "the first multicloning site", "the second promoter" and "a plasmid". There are insufficient antecedent bases for these limitations in the claim. Claims 27 and 28 are rejected for being dependent from the rejected claim 26 and also for failing to further clarify the basis of the rejection.

8. Claims 11-14 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, it is not clear from the language of claims 11 and 25 whether the expressed protein inhibits the proliferation of only the host cells grown at their suitable temperature or whether the expressed protein inhibits the proliferation of both the first host cells grown at their suitable temperature and of the second host cells having a growth temperature lower than that of the first host cells. Additionally, it is not clear from the language of claim 11 whether "said host cell" refers to the first host cell or the second host cell.

Claims 12-14 are rejected for being dependent from the rejected claim 11 and also for failing to further clarify the basis of the rejection.

9. Claims 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-28 recite the limitation "the first multicloning site". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Mujacic et al. (Gene, 1999, 238: 325-332, Applicant's IDS).

Mujacic et al. teach an expression vector for producing foreign proteins in *E. coli* cells, at a temperature between 15 and 23°C (i.e., a temperature below the suitable growth temperature of *E. coli* cells), wherein protein expression is induced with IPTG (i.e., inducing substance) (Abstract, p. 326, columns 1 and 2, p. 327, column 2 bridging p. 328, Fig. 1, p. 329, Fig. 3, p. 330, column 2, last paragraph and Fig. 3, p. 331, column

1). Since Mujacic et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

12. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Tutino et al. (Extremophiles, 2001, 5: 257-264, Applicant's IDS).

Tutino et al. teach isolation and characterization of a small, cryptic plasmid from Antarctic bacteria and the use of this plasmid to construct shuttle vectors able to replicate and express foreign genes when introduced into cold-adapted host cells (i.e., the foreign genes can be expressed at a temperature below the suitable temperature of a host other than the cold-adapted bacteria) (claim 1), wherein the foreign proteins are produced when the host cells are grown at 4°C (claims 2 and 3), and wherein foreign protein expression is controlled by the *lacZ* promoter (i.e., expression is induced with lactose, an inducing substance, as recited in claims 1-3) (Abstract, p. 257, column 2, p. 258, column 1, p. 260, column 1, p. 261, column 2 bridging p. 262, p. 263, columns 1 and 2). Since Tutino et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

13. Claims 1-3, 19, 21, and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Pelzer et al. (U.S. Patent No. 6,566,110), as evidenced by Whyte et al. (Appl Environ Microbiol, 1998, 64: 2578-2584) and Chiu et al. (J Biol Chem, 1999, 274: 20578-20586).

Pelzer et al. teach a replicative expression vector for inducible expression of foreign proteins in a bacterium of genus *Rhodococcus* (claims 1 and 19), wherein the expression vector comprises the tipA promoter, and wherein the expression from the vector is induced by thiostrepton (claim 21) (column 3, lines 1-7 and 30-38, column 25, lines 1-33). Pelzer et al. also teach their expression vector as containing additional genes that are to be introduced into the host cells, wherein these gene may be separately regulated (i.e., their expression driven from a separate promoter; claim 26) (column 23, lines 51-55). With respect to the limitations of the proteins being expressed at a temperature lower than the suitable temperature range of a host other than *Rhodococcus* (claim 1), wherein the temperature is 15°C or lower (claim 2) or 4 °C (claim 3), this is an inherent property of *Rhodococcus* cells, which ca be grown within a large temperature range from 0 °C to 35 °C (see for example Whyte et al., Abstract, p. 2579, column 1, third full paragraph, p. 2580, column 1). With respect to the limitation of the vector comprising a multicloning site (claim 26), this is an inherent property of any expression vector; all expression vectors have a multicloning site. Pelzer et al. also teach the limitation of an inducer cassette (claim 26) because: (i) they teach a separate promoter driving the expression of an additional genes (see above), wherein one of the additional genes must necessarily be *TipA*, because, in the absence of *TipA*, the thiostrepton / tipA promoter inducible system does not work (see Chiu et al., p. 20580, column 2, first full paragraph). With respect to the limitation of the vector comprising a thiostrepton resistance gene (claim 26), this again is an inherent feature of an expression vector comprising a thiostrepton / tipA promoter inducible system; in the

absence of such a gene, the host cell would die during the induction step. With respect to the limitation of the vector comprising a DNA region essential for autonomous replication in *Rhodococcus* (claim 26), since the replicative vector of Pelzer et al. is used in *Rhodococcus*, it must necessarily comprise this DNA region. Since Pelzer et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

14. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Hashimoto et al. (J Gen Microbiol, 1992, 138: 1003-1010).

Hashimoto et al. teach that expression of nitrile hydratase (NHase) in *E. coli* results in NHase accumulation into inclusion bodies and loss of enzymatic activity and that the expression of NHase in *Rhodococcus* results in the production of soluble enzyme (p. 1003, column 2). Hashimoto et al. teach obtaining their *Rhodococcus* expression system by screening *Rhodococcus* strains for plasmids and using these plasmids to construct an *E. coli- Rhodococcus* shuttle expression vector, wherein the shuttle expression vector is capable of expressesing NHase in *Rhodococcus* and wherein NHase expression is induced by the addition of methacrylamide (i.e., an inducing substance) (Abstract, p. 1003, column 2, p. 1004, column 2, p. 1005, columns 1 and 2, p. 1009, column 2, p. 1010, column 1). Since Hashimoto et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-3, 11-14, 19-21, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Mot et al. (Microbiology, 1997, 143: 3137-3147, Applicant's IDS), in view of each Takano et al. (Gene, 1995, 166: 133-137, Applicant's IDS), Olins et al. (Gene, 1988, 73: 227-235), Whyte et al., and Chiu et al.

De Mot et al. teach isolation of a criptic plasmid from *R. erythropolis* and the use of this plasmid to construct a shuttle *E. coli-Rhodococcus expression* vector (i.e., a vector comprising a DNA sequence essential to autonomous replication in *Rhodococcus* and a DNA sequence essential to replication in *E. coli*), wherein the vector can be used with a wide range of *Rhodococcus* species, including *R. erythropolis* (claims 1, 13, 14, 20, 21, 26, and 27) (Abstract, p. 3137, columns 1 and 2, p. 3138, column 1). De Mot et al. do not teach an inducible expression vector, wherein the inducing substance is thiostrepton (claims 1, 20, and 21) or TipA-LG10 promoter (claim 28). Takano et al. teach tipA promoter / thiostrepton inducible system to construct inducible expression vectors for expression of proteins in *Streptomyces* spp, wherein the inducible expression vectors also contain the thiostrepton resistance gene (claims 1, 21, and 26) (Abstract, p. 133, column 2, p. 134, column 1). Takano et al. also teach that such vectors can be used for induced expression of proteins that inhibit host cell growth

when the cells are gown at the suitable temperature (claims 11 and 25) (p. 133, column 2). Takano et al. do not teach *Rhodococcus, wherein Rhodococcus* is *R. erythropolis* (claims 13, 14, 20, 25, and 26) or TipA-LG10 promoter (claim 28). Olins et al. teach that the use ribosome-binding site derived from the region located upstream from gene 10 of the phage T7 (g10-L) in expression vectors dramatically increases the expression of a wide variety of foreign genes (Abstract, p. 228, column 1 bridging column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the expression vector of De Mot et al. by introducing the tipA promoter / thiostrepton inducible system of Takano et al. together with the thiostrepton resistance gene, with a reasonable expectation of success. Additionally, it would have been obvious to one of skill in the art, at the time the invention was made, to further modify the vector of De Mot et al. and Takano et al. by replacing the RBS of the tipA promoter with the g10-L of Olins et al. to obtain the *TipA-LG10* promoter, with a reasonable expectation of success (it is noted that the specification defines TipA-LG10 promoter as the TipA promoter and the RBS derived from lambda phage gene 10; see paragraph 0152). The motivation to use the tipA promoter / thiostrepton inducible system is provided by Takano et al., who teach that (i) inducible system should be used for expression of proteins that inhibit host cell growth, and (ii) tipA promoter / thiostrepton is a widely used and very efficient inducible system (p. 133, column 2). The motivation to use the thiostrepton resistance gene is also provided by Takano et al., who teach the need to provide resistance to thiostrepton upon induction (p. 134, column 1, first full paragraph). One of skill in the art would have been motivated to do so because Olins et

al. teach dramatic enhancement of protein expression by using g10-L. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such an expression vector because the art teaches that such expression vectors can be successfully made and used. With respect to the limitations of the proteins being expressed at a temperature lower than the suitable temperature range of a host other than *Rhodococcus* (claims 1 and 11), wherein the temperature is 15°C or lower (claims 2 and 25) or 4 °C (claims 3 and 12), this is an inherent property of *Rhodococcus* cells, which ca be grown within a large temperature range from 0 °C to 35 °C (see for example Whyte et al., Abstract, p. 2579, column 1, third full paragraph, p. 2580, column 1). With respect to the limitation of the vector comprising a multicloning site (claim 26), this is an inherent property of any expression vector; all expression vectors have a multicloning site. With respect to the limitation of an inducer cassette comprising a promoter driving the expression of the *TipA* gene (claim 26), the vector of De Mot et al. and Takano et al. must necessarily contain this because, in the absence of *TipA* gene product, the thiostrepton / tipA promoter inducible system does not work (see Chiu et al., p. 20580, column 2, first full paragraph). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

17. Claims 1-3, 11-14, 19-21, and 25-28 are rejected. Claims 4-10, 15-17, 22, 23, and 29-31 have not been further treated on the merits for being in improper form since a multiple dependent claim cannot depend from another multiple dependent claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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